REMARKS

The claims pending and under examination in this case are claims 23-25 and 27-41. The amended claims are now believed to be patentable.

The term "dinitro aniline" can have more than one meaning depending on the context. For example, it can refer to a family of pesticidal agents or herbicides as shown in the Compendium of Pesticide common names. (See exhibits for trifluralin and ethafluralin attached). These documents show that it is conventional to name a family of herbicides as " dinitroaniline" herbicides. This is so even if the "dinitroaniline" is not a specific compound as such but reference is made to compounds which are derived from a specific compound, namely 2,6-dinitro aniline.

The claims have been amended to clearly define the subject matter thereof, and recite the process steps and use proper format with antecedent bases, etc. Accordingly, the rejection of the claims under 35 U.S.C. § 112 is rendered moot by these amendments. Reconsideration and allowance of the claims is respectfully solicited.

At paragraph 2, page 2 of the Office Action, in responsive to the Examiner's question, if no antisublimating agent is added prior to lyophilization (the dehydration step) trifluralin will be removed from the formulations during this step. So it is imperative to add an antisublimating agent. This antisublimating agent can be a sugar but some of them are better for this purpose than others (page 6, line 26 of the present application). As can be seen on page 8, line 25 of the present application, trehalose is used in all the hydrating solutions in order to be present and protect trifluralin for being removed during the dehydration step. The rejection under 35 USC § 102(b) over WO 95/31970 is respectfully traversed.

The described method refers to processes of production of a saturated organic solution of lipid and an active agent that, upon addition of water, would become a liposomal formulation. This method does not produce liposomes. Liposomes can only be formed if the organic solvent is removed by any means. The only possible systems that can come out of that method are micelles.

By definition, liposomes are lipid vesicles consisting of one or more concentric sealed bilayers, dispersed in an aqueous environment. The presence of organic solvents will make it impossible to cause the formation of a bilayer structure.

Concerning novelty in the present application, any person skilled in the art knows how to prepare liposomes. These liposomes will obey a broad Gaussian distribution around the selected size for the preparation. The novelty of this application is that it predefines two different sizes according to the desired target organs (page 8, lines 1 to 9 of the present application). Liposomal formulations achieved by mixing two distinct liposomal populations with two distinct average sizes, obeying two distinct Gaussian distributions are never referred to or presented in the prior art.

Reconsideration of the rejection of the claims to the liposome formulation and the method of preparing the formulation and using it is respectfully solicited in view of the foregoing arguments and amendments.

The inventive step is that in spite of the thousands of publications in the field that are presented every year, for the first time the inventors of the present invention have discovered that mixing two distinct populations with predefined average sizes to reach different selected organs would be very beneficial to the treatment of diseases that could not be treated with only one liposomal population. It

is the case of leishmaniosis. The disease can be present in many organs such as liver, spleen, bone marrow and skin. Liver and spleen can be targeted with a liposomal population of mean size of 400nm that will not reach the bone marrow and the skin. In order to reach the bone marrow and the skin, simultaneously with the liver and the spleen, a liposomal population with the mean size of 50nm should be mixed with the one that has a 400nm mean size, ensuring in this way that the liver, spleen, bone marrow and skin will be able to reach the necessary amount of liposomes to achieve a therapeutic effect.

It is believed that the claims now define patentable subject matter and favorable action and allowance of the present application is respectfully solicited.

Should the Examiner wish to contact Applicants' representative, he may do so by telephoning Edward H. Valance, Reg. No. 19,896, at (703) 205-8000 in the Washington Metropolitan area.

Applicants respectfully request return of form PTO-1449 with initials by the Examiner if appropriate.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By: Edward H. Valence #19896
FOR Joseph A. Kolasch
Reg. No. 22,463
P. O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

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Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKING TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 24. (Amended) The liposomal formulation according to claim 23, which comprises a mixture of pre-defined populations of particles with mean diameters respectively bigger than 400nm and lower than 100nm.

Claim 25. (Amended) A process for the preparation of a final formulation composed [plurality] of distinct populations [of liposomal formulations of particles] with distinct mean diameters, containing [one dinitroaniline] a dinitro aniline pesticide, which comprises the steps:

[(1)] 1. [obtention] obtaining of the liposomal formulations containing vesicles of [dinitroaniline] dinitro aniline pesticide by hydration, with a solution containing an antisublimating agent of a lipidic film containing the [dinitroaniline] dinitro aniline pesticide;

2. Obtaining different populations with well-deinfed diameters by a sizing step;

3. mixing the distinct populations;

[(2)] 4. lyophilization [and] dehydration of the [dinitroaniline] so obtained liposomal formulations; and

[(3)] 5.rehydration of the dehydrated liposomal formulations.

Claim 28. (Amended) The process according to claim 25, wherein the hydration is carried out by the addition of [a small amount] an aliquot portion of an aqueous solution, followed by the addition of the remaining volume of the aqueous solution, after a resting period.

Claim 29. (Amended) The process according to claim 28, which comprises using, in the hydration steps, a [non-saline] salt-free solution.

Claim 30. (Amended) The process according to claim 29, which comprises performing the rehydration steps with saccharose, trehalose, glucose or [any other sugar solution] mixtures thereof.

Claim 32. (Amended) The process according to claim [31] 25, which comprises mixing particles after sizing to yield a population of particles with diameters of, respectively, bigger and lower than 100 nm.

Claim 34. (Amended) The process according to claim [31] 25, which comprises performing the hydration by addition of a small amount of aqueous solution, namely 20% of the final volume, followed by addition of the rest of the volume, namely 80% of the final volume, after a 30-minute rest period.

Claim 35. (Amended) The process according to claim [31] 25, which comprises using in the hydration step a [non-saline] salt-free solution.

Claim 36. (Amended) The process according to claim [31] 25, which comprises performing rehydration [using] with a member selected from the group consisting of solutions of saccharose, trehalose, glucose [or another sugar] and mixtures thereof.

Claim 37. (Amended) The process according to claim 31, which comprises using at least one of the lipids selected from the group consisting of distearoylphosphatidylcholine (DSPC), phosphatidylcholine (PG), cholesterol (Chol) [or] and Chol derivatives, sphingomielin (SM), dioleoylphosphatidylcholine (DOPC), dioleoylphosphatidylglycerol (DOPG), phosphatidylglycerol (PC), dimiristoylphosphatidylcholine (DMPC), dipalmitoylphosphatidylcholine (DPPC), gangliosides, ceramides, phosphatidylinositol (PI), phosphatydic acid (PA), dicetylphosphate (DcP), dimiristoylphosphatidylglycerol (DMPG), stearylamine (SA), dipalmitoylphosphatidylglycerol (DPPG) and mixtures thereof.

Claim 38. (Amended) The process according to claim 31, wherein the [dinitroaniline] dinitro aniline pesticide comprises trifluralin.

Claim 39. (Amended) A liposomal formulation [according to claim 23, when prepared] containing a dinitro aniline pesticide when prepared by [the] a process according to claim 25.

Claim 40. (Amended) A method of using the liposomal formulation as defined according to claim 23 [for] which comprises the treatment of disease in humans or animals, [which comprises] wherein administration of a therapeutic quantity of the [dinitroaniline] liposomal formulation is applied to humans or animals.

Please add the following new claim:

41. Use of liposomal formulations for the preparation of a pharmaceutical formulation for the treatment in humans or animals, characterized by the use of a therapeutic efficient quantity of the pharmaceutical formulation containing a dinitroaniline liposomal formulation according to claim 39.